REMARKS

I. Claim Status. Claims 1-4 and 7-19 are currently pending and under consideration. Claims 5, 6 and 20-35 are canceled.

Claims 1 and 7-9 have been amended to delete the word "about" in the phrase "about 6." Support for this amendment is found in the specification as filed at, *e.g.*, page 10, line 30 and claims 6-9 as originally filed. Therefore, no new matter is added by way of these amendments.

Reconsideration of the claims is respectfully requested.

II. Amendments to the Specification. The specification has been amended to provide the SEQ ID NOs. for peptides KREAEAEF, EAEAEF, and EAEF. By this amendment, no new matter is added to the specification.

III. Objections to the Specification. The Examiner has objected to the specification for allegedly failing to provide proper antecedent basis for limitations of the length of peptide epitopes, such as "about 6 to about 45," as was recited in the original claims as filed.

The attention of the Examiner is directed to the Office Action issued in the instant application on February 1, 2005, which raised an identical objection. This objection was addressed in the Amendment in Response to Non-Final Office Action filed by Applicants on July 1, 2005 by amending the specification to include a paragraph with the epitope lengths of original claims 6-9. Therefore, withdrawal of this objection is respectfully requested.

The Examiner has objected to the specification for allegedly failing to comply with the Sequence Rules of 37 CFR 1.821-1.825. The Examiner states that the specification must be

reviewed for compliance to these rules and cites the specification at page 50, line 26 and Table 2 on pages 50-51 for failing to identify sequences by SEQ ID NO.

In response, the specification has been amended to recite SEQ ID NOs for the peptide at page 50, line 26 and additional peptides at page 49, line 29 and page 50, line 23. A new Sequence Listing is submitted herewith to include the sequence KREAEAEF (SEQ ID NO: 99). No new matter is added by way of this amendment.

Regarding Table 2, the Examiner is directed to the footnote directly following the table on page 52. The footnote gives the SEQ ID NOs for the N-terminal amino acids of the listed sequences in the "Assumed sequence" column. Thus, sequence identifiers are provided.

Based upon the above, the objections to the specification have been obviated. Withdrawal of the objections is respectfully requested.

III. Claim Rejections.

(i) Rejections Under 35 U.S.C. §112, first paragraph (enablement). The Examiner has rejected claims 1-4 and 7-19 under 35 U.S.C. §112, first paragraph for allegedly failing to satisfy the enablement requirement. The Examiner alleges that the specification as filed does not provide enablement due to (1) ambiguity of the term "about 6," (2) unpredictability of maintaining structure upon inserting or substituting amino acids, (3) inoperability of small peptide sequences, especially those under 9 amino acids in length, and (4) difficulty in identifying homologous sequences and unpredictability concerning reduction of IgE binding/allergenicity. These rejections are traversed and overcome each in turn, below.

The Examiner alleges that the term "about 6" is ambiguous and could read upon epitopes less than 6 amino acids in length. In response, without conceding the validity of the

rejection, claims 1 and 7-9 have been amended to replace the term "wherein the peptide epitope sequence is about 6 to..." to recite "wherein the peptide epitope sequence is 6 to..." The basis of the rejection has been addressed. Withdrawal of the rejection is respectfully requested, accordingly.

The Examiner alleges that the specification does not provide enablement for the hybrid proteins claimed due to the unpredictability of maintaining structure upon inserting or substituting amino acids, especially since the epitopes are not described as linear or conformational. Regarding the insertion versus substitution of amino acids, it is known that homologous proteins with identical biological functions and >30% sequence identity can share nearly identical structures. It is also well known that sequence identity of homologous proteins is concentrated mainly in the compact core (scaffold) region of their structures, and their sequence difference is mainly in the loop region. Loop and corner regions can especially tolerate sequence substitutions and insertions since it is the scaffold region that maintains the native structure. Also, allergenicity of a protein depends on the interaction of its multiple B cell epitopes with specific antibodies. The epitopes may consist of only residues in the loop region or a mixture of residues from loop region and surface-accessible scaffold region. Sequence changes in the loop or scaffold regions of hybrids may alter the nature of epitopes, which effectively reduces the epitope density of the allergen protein with accompanying reduction in allergenicity when measured with antibodies specific for the allergen protein. Finally, immunogenicity of hybrids will not change, as epitope density of the scaffold protein of the hybrids remains the same as the original scaffold protein. Therefore, it is well known in the art that either insertion or substitution would allow the hybrid to maintain the structure of the scaffold protein while providing for a reduction of allergenicity with the retention of immunogenicity.

Regarding linear versus conformational epitopes, the Examiner states,

> Since by definition discontinuous or conformational epitopes include amino acids widely separated in the primary amino acid sequence and since it is not reasonable that a 6 amino acid peptide includes widely separated amino acid residues, such epitopes are linear determinants (Office Action at page 7, lines 7-10).

However, whether the claimed epitopes are or are not linear, conformational, or some combination is of no consequence regarding the enablement requirement and does not need to be described in the specification. The specification teaches how to make and use the claimed hybrid allergens and includes examples showing that the epitopes elicit an immunological response but reduced allergenic response. The mechanism by which the hybrids elicit the response need not be known. Hence, whether the epitopes are or are not linear, conformational, or a combination is not relevant to the question of whether the claims are enabled. The Federal Circuit has clearly stated that the standard applied is that one of ordinary skill in the art should be able to make and use the invention without undue experimentation (*see In re Wands*, 858 F.2d 731, 737 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) and M.P.E.P. § 2164.01). One need not know the mechanism of action to make and use an invention, and knowledge of the mechanism is therefore not required to enable the claimed subject matter.

The Examiner also maintains that, due to the non-working example in the specification of an 8 amino acid peptide epitope, the specification does not provide enablement for peptide epitopes of less than 9 amino acids. In first response, the standard of enablement is not that all of the encompassed embodiments of the claims be exemplified by working examples but that all of the encompassed embodiments be enabled by the specification. Also, the Examiner states that in the same paragraph quoted by Applicants (Harlow at page 76, paragraph immediately following "Size of Peptide" section title), Harlow states that 10 amino acids should be used as the lower limit. The Examiner's reading of Marlow is not well taken. Ten amino acids are what are optimal; 6 amino acids still will work. This does not mean that undue experimentation is required to obtain an

antibody response to peptides that are 6 amino acids in length. Harlow states that "With peptides of 6 amino acids or slightly larger, the responses vary. Some will generate good antibodies and some will not" (Harlow, page 76, paragraph immediately following "Size of the Peptide"). Thus, a fair reading of Harlow is that peptides of 6 amino acids in length can be used to generate antibodies. Moreover, the present application for methods of creating hybrids comprising an epitope of peptides, *e.g.*, 6 amino acids in length, using such hybrids as immunogens, and determining which hybrids generate an immune response to the epitope. Accordingly, one of ordinary skill in the art can practice the claimed invention with hybrids comprising epitopes of 6 amino acids without undue experimentation. Thus, the full breadth of the claims is enabled.

The Examiner also alleges that the specification is not enabling as to how an allergen protein that is structurally homologous to a scaffold protein is to be selected. The Examiner contends that no parameters for selection are given, there is unpredictability in how mutations change structure or IgE response, the claims read upon endogenous/self proteins that would not elicit a response, and that allergenicity can not be determined *a priori* on a structural basis. The Examiner's position is not well taken. The claims recite that the allergen hybrid protein has reduced allergenicity but retains immunogenicity. Thus, a hybrid that does not elicit a response (such as self proteins) would not be covered by the claims. It would be routine for one of ordinary skill in the art to determine if a hybrid has reduced allergenicity with retention of immunogenicity as outlined in the Examples of the specification, *e.g.*, Examples 5 and 6 show the identification of the IgE dominant epitopes of an allergen. Furthermore, "structural homology" is defined in the specification at page 18, lines 22-25:

> Proteins are structurally homologous when, due to primary sequence similarity, they adopt a similar core secondary and tertiary structure so that their three-dimensional structures can be superimposed with almost complete (greater than 70%) overlap. Their surface tertiary structure, however, may vary.

One of ordinary skill in the art would understand, through this definition, how to select potential protein candidates, even if *a priori* allergenicity is not determined. Furthermore, the standard for enablement is not lack of any experimentation but lack of undue experimentation. Once a protein candidate is selected, it would be routine for one of ordinary skill in the art to determine if a hybrid has reduced allergenicity with retention of immunogenicity, as stated above.

The specification fully enables one of ordinary skill in the art to make and use the invention as claimed. Therefore, the rejection under 35 U.S.C. §112, first paragraph for enablement is obviated, and its withdrawal is respectfully requested.

(ii) Rejections Under 35 U.S.C. §112, first paragraph (written description). The Examiner has rejected claims 1-4, 7-13, and 17-19 under 35 U.S.C. §112, first paragraph for allegedly failing to satisfy the written description requirement. The Examiner contends that the specification does not disclose a core structure that would retain immunogenicity but reduce allergenicity and that the specification does not disclose how to select structurally homologous proteins. This rejection is traversed.

Regarding structurally homologous proteins, the Examiner is directed to the specification at page 18, lines 22-25, cited above. The specification describes what structurally homologous proteins are and, therefore, describes how to select proteins that are structurally homologous. The specification at page 18, lines 22-25 states that a structurally homologous protein is one that adopts a structure such that there is a 70% or more three-dimensional structural overlap with another protein based on the core secondary and tertiary structures of the proteins, due to primary sequence similarity, notwithstanding that the surface tertiary structures may be dissimilar. However, the Examiner states that the criteria of comparison to be used with solved X-ray crystal structures and computer-based alignments useful in identifying homologous sequences (Office

Action at page 12, lines 1-4) are apparently not disclosed. Upon reading the specification, one would recognize that it is the structures of the cores of the proteins that are being compared, allowing for variations in the surface structure. As long as the atoms of the secondary and tertiary structures of the cores of the proteins overlap by 70% or more, one of ordinary skill in the art could make and use the invention based on the specification.

The Examiner also states that sequence identity of 50% does not guarantee structural similarity. In response, the Examiner's attention is again directed to the specification at page 18, lines 22-25: structural homology, as recited in the claims, is defined as based on 70% or more three-dimensional structural overlap, not based on sequence identity. This structural overlap, as defined, is due to a sequence similarity, but it is the structural overlap that defines structural homology, *i.e.*, the similarity may be any similarity and may be quite low. Indeed, "homologous" (as opposed to "structurally homologous") is defined in the specification at page 18, lines 11-14 based on sequence identity of 30% or greater. Within this same paragraph at page 18 (lines 11-21), the specification notes that the scaffold and allergen proteins should not have too high a sequence identity, otherwise allergenicity of the hybrid may result. Thus, the specification contains a definition of structurally homologous that compares proteins based on structure, not sequence identity. If the primary sequences are 50% identical, or any other percentage identical, this does not matter: what is being compared, as recited in the claims as defined in the specification, is structural homology.

The Examiner also states that single point mutations can lead to surprising alterations in protein structure and activity. However, as long as the allergen and scaffold proteins are structurally homologous, the sequence similarity does not matter, as explained above. Therefore, should a single point mutation disrupt structure beyond the definition of structurally homologous as

described above, the protein would fall outside of the claims. As for a change in activity, the activity as recited in the claims is to maintain immunogenicity while reducing allergenicity. Any change in the endogenous activity of the original protein is irrelevant. It is the function of the hybrid protein at issue: As described above, one of ordinary skill in the art could, without undue experimentation based on the description in the specification, determine whether any given hybrid performs its function of retaining an immunological response with a reduced allergenic response.

To address the issue of a core structure, the Examiner is directed to the hybrid allergens claimed, as recited in independent claims 1 and 17. Claims 1 and 17 recite that the hybrid allergens have reduced allergenicity while maintaining immunogenicity and have an epitope of an allergen that is structurally homologous to a scaffold protein where the hybrid protein maintains a native conformation and the epitope is present in a surface accessible region of the hybrid protein corresponding to its position in the allergen protein. These are defining characteristics that are both functional and structural. The specification at page 17, lines 8-21 describes that the epitope sequence may be introduced into a loop or corner of a surface region. Furthermore, Tables 8 and 9 beginning on pages 100 and 135 of the specification, respectively, show examples of known allergens and that the structures of many of these allergens are also known. Therefore, upon reading the specification, one would recognize that the defining characteristics as recited in the claims and specification relate to the structure and function of the hybrid proteins and provide sufficient characteristics to identify a general genus of hybrids. A "core structure," as defined by the Examiner, *i.e.,* a core protein structure, is not required. In fact, the Examiner cites the Federal Register and states that a claimed genus meets the written description requirement

> by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the

genus" (Office Action at page 12, lines 13-17, citing Federal Register, Vol. 66, No. 4, pages 1099-1111).

The claims recite a combination of both structural and functional identifying characteristics that, upon reading the specification, one would recognize as defining a genus of allergen hybrid proteins.

The Examiner again states that the presence or absence of allergenicity can not be determined *a priori* on a structural basis and that it is unknown how changes to an epitope sequence will change IgE binding. The specification is required to have written description for the claims as written. The specification does not need to describe every variation of the invention outside the scope of the claims. As described above, the specification fully supports the claims as written. Structural homology and the eliciting of an immunological and a reduced allergenic response are recited in the claims. Should a protein not show structural homology, as defined above, or reduced allergenicity and retained immunogenicity, the protein would fall outside of the claims. Therefore, the specification need not describe subject matter that lies outside of the scope of the claims. The specification is only required to provide sufficient written description for what is claimed, which it does as explained in detail above.

In view of the above arguments, it is believed that the rejection for written description has been traversed and should be withdrawn.

(iii) Rejections Under 35 U.S.C. §§102 and 103. Applicants acknowledge that the previous rejections raised under 35 U.S.C. §§102 and 103 have been withdrawn.

CONCLUSION

In view of the above remarks, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue.

If there are any other issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

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Respectfully submitted,

By _____

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